REMARKS

With the entry of the present Amendment, claims 37, 41-43, 49, 52-53 and 59 remain in this application. Claims 37, 41-43 and 59 have been examined; claims 49 and 52-53 have been withdrawn. Claim 37 has been amended to expedite prosecution. Claim 49 has been amended to be to be of the same scope as claim 37. Claims 38-40, 44-48, 50-51, 54-58 and 61 have been cancelled without prejudice. None of the amendments made herein constitutes the addition of new matter.

The Rejections under 35 U.S.C. 103(a)

Claims 37 and 41 remain rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Bayburt et al. (1998) in view of Barnes et al. (1999). Applicants respectfully traverse this rejection.

Applicants traverse the rejection because the cited references do not teach or suggest nanoscale particles comprising artificial (non-naturally occurring) membrane scaffold proteins or in combination with G protein coupled receptors, there is no motivation in the references to make the claimed combination of elements, and the references fail to provide the requisite expectation of success to make a *prima facie* case for obviousness. Each of the noted points is independently and legally sufficient to require the withdrawal of the rejection.

The cited Bayburt reference is said to teach the reconstitution and imaging of a membrane protein (NADPH cytochrome P450 reductase) in a nanometer size phospholipid bilayer stabilized with apolipoprotein A-1. The Patent Office has acknowledged that this reference fails to teach the incorporation of a G protein coupled receptor (GPCR) such as a 5-hydroxytryptamine (5-HT) receptor. The cited Barnes reference is said to teach the structures and biological functions of 5-HT receptors and a "high level of interest" in the actions of 5-HT and its role in potential therapy, with the Patent Office alleging that it would have been obvious to one of ordinary skill in the art to

reconstitute a 5-HT receptor in a nanometer size phospholipid bilayer as taught by Bayburt with a reasonable probability of success.

The present claims encompass nanoscale particles comprising artificial membrane scaffold proteins neither taught nor suggested by the cited Bayburt reference. The context of the present application is clear that the "artificial" membrane scaffold proteins do not occur in nature. Applicants respectfully note that the Bayburt paper describes particles prepared using cytochrome P450 reductase, a protein in which only one segment is within the cell membrane in nature and which protein is not a G protein coupled receptor, and **naturally occurring** human apolipoprotein A-1; see also Jonas et al. (1989) J. Biol. Chem. 264:4818-4824, already of record, where it is made clear that the Bayburt paper relates to apolipoprotein prepared from human plasma (i.e., naturally occurring). By contrast, the present application relates to artificial membrane scaffold proteins, as described at pages 20 and 26 of the as-filed Specification. The artificial membrane scaffold proteins of the present invention are clearly distinguished in structure from the naturally occurring human protein, for example, in the (artificial) membrane scaffold protein sequences, certain helices of native apo A-1 are repeated, deleted or replaced with other helices, or have truncations, or have altered hinge regions. See page 14 of the as-filed Specification, page 20 which refers to mutagenesis and directed evolution of the MSPs and page 25, which discusses linker sequences and minimization of linker length and other structural features. The choice of particular artificial MSPs allows better control of particle size and improved uniformity in size (see page 28, line 20 et seq, page 4, lines 21 et seq, and page 29, line 1 et seq. With the current amendment, it is recited that the artificial membrane scaffold protein lacks an N-terminal globular domain of apolipoprotein A1. Bayburt fails to teach or suggest any such structural alterations in natural apo A-1, such as the absence of an N-terminal globular domain, as recited in the claims as amended,

In the interest of advancing prosecution and without acquiescing to the rejections, claim 37 has been amended to recite that the artificial membrane scaffold protein lacks a globular domain of human apolipoprotein. All of the specifically exemplified MSPs lack

the N-terminal globular domain of the naturally occurring human apolipoprotein A1. This amendment is inherently supported by the present application – all the specifically exemplified lack the sequence corresponding to the first 43 N-terminal amino acids of mature human apolipoprotein A1. The specification at page 2, notes the presence of a globular domain in the native apolipoprotein A1 structure. A comparison of the specifically exemplified artificial MSP sequences with that of the apolipoprotein sequence supports this amendment.

Furthermore, the cited Bayburt reference makes no teaching or suggestion that a protein with more than a single segment inserted into a membrane or nanoscale discoid particle should be or could be successfully incorporated into a nanoscale particle, nor does this reference teach or suggest that any membrane scaffold protein structures could be designed for use together with GPCRs in nanoscale discoid particles. The GPCRs are significantly more complex with respect to membrane association (7 transmembrane segments) than is cytochrome P450 reductase (a single protein segment associated with the membrane).

As noted above, the cited Barnes reference makes no suggestion of any GPCR could be combined with an artificial (or even a natural) membrane scaffold protein in a nanoscale disc-like particle. Applicants' own disclosure cannot be the source of the motivation to combine elements; i.e., the Patent Office cannot make a hindsight reconstruction of the claimed invention. The courts have taken the position that the motivation for combining references in the formulation of a rejection for alleged obviousness must come from within those references. (See, e.g., ACS Hospital Systems, Inc. v. Montfiore Hospital, Inc., 221 U.S.P.Q. 929, C.A.F.C., 1984; Northern Telecom, Inc. v. Datapoint Corp., 15 U.S.P.Q.2d 1321, 1323 (Fed. Cir. 1990); In re Oetiker, 24 U.S.P.Q.2d 1443 (Fed. Cir. 1992) ("[t]here must be some reason, suggestion, or motivation found in the prior art whereby a person of ordinary skill in the field of the invention would make the combination" and "[t]hat knowledge can not come from the applicant's invention itself."); and In re Dow Chemical Co., 5 U.S.P.Q.2d 1529, 1531 (Fed. Cir. 1988). This aspect of traverse provides a legally sufficient basis for withdrawal of the

rejection under Section 103. The courts have further cautioned against the impermissible use of hindsight in evaluating patentability. Neither reference suggests combining a GPCR with any membrane scaffold protein in a nanoscale particle. Therefore the rejection is not proper and must be withdrawn.

Similarly, neither cited reference makes any suggestion that it would be possible to incorporate a protein with so complex a membrane interaction as a GPCR into a nanoscale particle, that the apolipoprotein A1 primary structure could be modified or that native ligand binding of a GPCR could be or would be maintained in a nanoscale particle such as taught and claimed in the present application. There is nothing in the cited references that would provide the requisite reasonable expectation of success in carrying out the invention as claimed. In contrast to the cytochrome P450 reductase, which has only one segment inserted into the membrane bilayer, the GPCRs have multiple transmembrane domains which are in intimate association with the membrane bilayer (and within the nanoscale discoid particles of the present invention). There is nothing in the cited references that provides any reasonable expectation of success for combining a protein with such complex interactions with a lipid bilayer as a GPCR so that the functional properties of the protein (e.g., ligand binding) and the stability and solubility of the nanoscale particle would be maintained (see, for example, In re O'Farrell, 7 U.S.P.Q. 2d 1673, Fed. Cir. 1988). This provides another legally sufficient ground for the withdrawal of the rejection under Section 103.

In addition, in the interest of advancing prosecution and without acquiescing to the rejection, Applicants have now amended claim 37 to recite that the artificial membrane scaffold proteins, lack the N-terminal globular domain of the naturally occurring apolipoprotein A1. Neither of the cited references teaches or suggests the use of such engineered membrane scaffold proteins as taught in the present application.
(Supported at pg. 19, lines 26-27)

In addition, Applicants have provided a Declaration of Daniel Oprian, Ph.D., an expert in the area of G-protein coupled receptors. This Declaration indicates the need in the art for a viable system with which to study and purify G-protein coupled receptors and

it also provides Dr. Oprian's opinion that the Bayburt provides no evidence that GPCRs could be successfully incorporated into nanoscale disc-like particles together with a membrane scaffold protein which is not identical to the naturally occurring human apolipoprotein A1. This Declaration is provided, along with his Curriculum Vitae, as Exhibit A.

Exhibit B, provided herewith, is a copy of a "News Item" from Science, vol. 304, pg. 674, which provides recognition of the nanoscale disc-like particles. Science is a prestigious refereed journal, in which information is selected for its importance and dissemination beyond the particular relevant field, i.e., that information must be new and exciting enough to merit presentation to scientists of other fields as well as the directly relevant field. This article states that "studying such gatekeepers (GPCRs) is extremely difficult, because removing them from the cell membrane almost invariably alters their shape and destroys their function". Robert Hamers, a faculty member of the university of Wisconsin, states" it"s a very cool technique.... I can see all kinds of applications for something like this." Attesting to the need in the art for the system of the present invention, Hamers was attributed with saying that "nanodiscs could shed light on the biochemical behavior of a host of membrane proteins that have escaped detailed understanding".

Andrew Leitz, a graduate student in the Sligar laboratory, presented his work with the incorporation of the β-adrenergic receptor (a GPCR) in nanoscale particles together with an artificial membrane scaffold protein, at the Protein Society's 17th Annual Symposium held July 26-30, 2003. His presentation won the Protein Society Annual Eli Lilly Poster Award for the best presentation by a graduate student. Thus, the work merited accolades from outstanding scientists in the field. A copy of the award is attached as Exhibit C.

In addition, the scientific community has responded to publications related to the membrane scaffold protein/nanodisc technology with many requests for material from the University of Illinois. Attached as Exhibit D is a Declaration of Roger W. VanHoy, a

Technology Manager in the Office of Technology Management at the University of Illinois. He notes that of the 233 fully executed Material Transfer Agreements during the last 28 months, 33 of those were for nanoscale particles and/or membrane scaffold proteins from the Sligar laboratory. This number represents about 15% of those fully executed Material Transfer Agreements; Dr. Sligar is one of an estimated 1200 faculty members whose work might be expected to lead to a request for transferred materials. An additional 4 requests for such materials are currently pending but not yet complete. This strong demand for materials of the present invention reflects the long felt need in the art for these materials.

In view of the foregoing arguments and amendments, Applicants respectfully maintain that the invention as claimed is not obvious over the cited art, and the withdrawal of the rejection is respectfully requested.

Request for Rejoinder

Applicants respectfully request the rejoinder of claims 49 and 52-53, which have been amended to be of the same scope as claim 37 (as amended). Applicants request that the particle and the method of making same should be found allowable.

Conclusion

Applicants respectfully submit that the pending claims are in condition for allowance and early notification thereof is requested.

If, in the interest of expediting prosecution, the Examiner has questions or comments, he is invited to telephone the undersigned at the indicated telephone number.

This Amendment is accompanied by Exhibits A-D. It is believed that the present submission does not necessitate a petition for extension of time or the payment of any fees under 37 C.F.R. 1.16-1.17. If this is incorrect, however, please consider this response to include the petition for the time necessary for a timely response and charge

any deficiency or credit any overpayment in fees pursuant to the foregoing Rules to Deposit Account No. 07-1969.

Respectfully submitted,

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